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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/444,791 05/19/95 BROCKHAUS

M 9191

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18M2/0212

NISEN

ART UNIT

PAPER NUMBER

1806

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/444,791

Applicant(s)
Brockhaus, et al.

Examiner
T Michael Nisbet

Group Art Unit
1806



☒ Responsive to communication(s) filed on May 19, 1995

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 44-61 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 44-61 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) 07/580,013

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

III. DETAILED ACTION

1. Applicant is reminded of the need to update the status of the previous parent applications
2. Claims 1-43 have been cancelled. Claims 44-61 were submitted in the preliminary amendment filed 5/19/95. Claims 44-61 are currently under consideration.
3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.
4. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. § 119. The certified copies have been filed in parent application, Serial No. 07/580,013, filed on September 10, 1990.
5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

7. Claims 44-61 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited TNF binding protein DNA sequences disclosed in the specification. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicant's claims as presently submitted, contain reference to the open term "comprising". Such open language is without limit to the moieties which can be added to either side of the molecule. Applicants are entitled to the fusion of routine elements to the claimed proteins. However, the fusion of any protein or any amino acid is not enabled. While addition of leader sequences etc. might not require undue experimentation, the addition of anything is not reasonable because applicants have no guidance as to what biochemical parameters are necessary to consider in adding foreign proteins. For example, fusion of the TNFr of the instant claims to other cytokines or other active molecules requires the consideration of the effect each biological activity will have on the other (ie. additive or inhibitory). In order for the rountineer to be able to use the invention as claimed, some guidance regarding the interaction of such different activities is needed.

The use of the word "binding protein" is an inherently functional word which requires only the functionality of the proteins. The use of such a functionality, ie. binding, as the single patentable distinction in the claim language allows for any inhibiting protein of a certain molecular weight to be encompassed by the specification. SDS-PAGE is simply not accurate enough to provide sufficient guidance to teach one of ordinary skill in the art how to make and/or use the full scope of the

invention as claimed. In fact, SDS-PAGE is only accurate to +/- 10 kd; thus the present description fails to distinguish one species of TNFr from one another.

Alternative language which could alleviate the problems might be drawn to the particular sequences disclosed in the specification. Absent such a sequence, undue experimentation would be required to practice the invention as claimed.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 51 is rejected under 35 U.S.C. § 102(b) as being anticipated by Capon (WO89/02922).

Claim 51 defines the invention as a DNA sequence which hybridizes to the DNA sequence of claim 48. Claim 48 defines a DNA sequence comprising the 55 kd subunit of the TNF binding protein and a "constant region of the heavy chain of a human immunoglobulin other than the first domain of said constant region".

Therefore, claim 51 encompasses any fragment of the sequence set forth in claim 48 that will hybridize to the claim 48 sequence because any sequence will hybridize to itself. The F_c region of the human heavy chain immunoglobulin sequence as set forth in Capon meets this test. Note the Capon patent at page 6 at fig. 4a-b and fig. 4a and 4b where a human constant region sequence is taught. Consequently, because applicant's claimed invention encompasses all sequences which hybridize to the

sequence of claim 48 and because an F_c region will hybridize to itself, the Capon patent anticipates the invention as claimed.

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

11. Claims 48-55 and 58-61 are rejected under 35 U.S.C. § 103 as being unpatentable over Wallach et al. in view of Capon et al. [WO 89/02922].

Briefly the claims are directed to a recombinant TNF fusion protein containing heavy chain human immunoglobulin sequences, and antibodies to the TNF protein and fusion protein. Wallach et al. teach a homogeneous preparation of a human

tumor necrosis factor receptor, see entire document. Note that, the Wallach et al. teach salts, functional derivatives and active fractions of the TNF receptor which would inherently include insoluble preparations, see abstract. Wallach et al. teach a 40-80 kDa protein determined by gel filtration which would reasonable be approximately 55 kDa by nonreducing SDS-PAGE. Wallach et al. teach a partial sequence of the TNF receptor protein on page 3. This sequence is exactly the same as amino acids 12-27 disclosed in figure 1. It therefore appears that Wallach et al. have the same protein as claimed. Wallach et al. teach a homogeneous protein obtained by recombinant methods, see pages 8-11. Wallach et al. teach a 40-80 kDa protein determined by gel filtration which would inherently be approximately 55 kDa by nonreducing SDS-PAGE. Wallach et al. teach a partial sequence of the TNF receptor protein on page 3. This sequence is exactly the same as amino acids 12-27 disclosed in figure 1. It therefore appears that Wallach et al. have the same protein as claimed. Wallach et al. teach a homogeneous protein obtained by recombinant methods, see pages 8-11. Wallach et al. does not teach a TNF fusion protein with a human immunoglobulin constant domain. However, Capon et al. teach adhesion variants. These variants contain active regions of protein molecules fused to the N-terminus of the constant region of immunoglobulin in place of the variable region(s) - retaining at least functionally active hinge, CH2 and CH3 domains of the constant region of an immunoglobulin heavy chain, see page 10. Capon et al. teach suitable companion immunoglobulin combining sites and fusion partners are obtained from IgG-1, -2, -3 or -4 subtypes IgA,

IgE, IgD or IgM, see page 13. Capon et al. teach that successful strategies in the development of drugs for the treatment of many receptor mediated abnormalities has been the identification of antagonists which block binding of the natural ligand. Since adhesions are normally present only on cell surfaces, it would be desirable to produce adhesions in a form which is more stable in the circulation. Therefore it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Wallach et al. to those of Capon et al. in order to obtain a soluble TNF-immunoglobulin fusion protein for the treatment of TNF related pathologies.

Finally, Capon teaches at page 30, example 1, the use of a published sequence for a protein to isolate the corresponding gene. Note the teaching where the sequence for CD4 is disclosed in Maddon et al and the probes were then generated and used to obtain the gene. Likewise, the instant rejection provides the sequence of the protein in Stauber et al.. All one of ordinary skill in the art would have to do is substitute the primers generated by Maddon with the primers generated from Stauber and one of ordinary skill would obtain a gene for the claimed sequence in fig. 1 of the specification. One of ordinary skill in the art would have been motivated to do so by the increased serum half-life which is associated with Ig fusion proteins argued in the previous paragraph. Furthermore, one of ordinary skill in the art would have been motivated to produce the TNF-Ig fusions recombinantly because of the increased purity of the products associated with recombinant protein expression. Furthermore,

Capon's Ig fusions are produced recombinantly. Therefore, given the reasonable expectation of success enjoyed by Capon with CD4, one of ordinary skill in the art would have been motivated to repeat the same successful methods. Consequently, one of ordinary skill in the art clearly would have been motivated to produce the claimed fusion proteins recombinantly at the time the invention was filed.

12. Claims 44-47 and 56-57 are rejected under 35 U.S.C. § 103 as obvious over Stauber et al. [JBC 263(35):19098-19104 (1988)] in view of either Lee or Wozney.

The invention as claimed recites a homogenous TNF binding protein which has a molecular weight of "about 55kd". The dependent claims limit the binding protein to the sequence set forth in Fig. 1.

Stauber et al. teach a homogeneous preparation of a human tumor necrosis factor receptor, see entire document. Note that the receptor is insoluble, but is solubilized by a variety of detergents with full retention of binding activity, see page 19099, column 1. While the protein of the reference was not obtained by recombinant methods, it nevertheless appears to be the same. The purification or production of a protein by a particular process does not impart novelty to a protein when the same protein is taught by the prior art.

Both Lee and Hawley teach the ability to use a protein to isolate and purify the gene. The Lee reference teaches the cDNA cloning of urate oxidase. The procedure involves only partial amino acid sequence information for the generation of PCR amplified primers which are then used to generate a probe to the first five amino

acids. See fig 1B. Moreover, the cloning of the urate oxidase cDNA is taught to be "generally applicable" and is useful for generation of full length sequences (see abstract). Further, the Lee reference specifically teaches at 1285, middle column, second paragraph the protein can be purified to homogeneity. The reference provides an available method for so purifying the target protein. One of ordinary skill would merely be required to apply the techniques used by Lee on urate oxidase, to the protein set forth in Stauber.

The Wozney reference specifically teaches "methods for designing oligonucleotide probes from protein sequence, and the use of these oligonucleotides to isolate the gene or a cDNA." (c.f. page 738, second para.). Page 739 goes on in the second paragraph, to outline the method of designing and using a probe to isolate a gene of choice. Accordingly, both Lee and Wozney teach one of ordinary skill in the art the feasibility of using a purified protein to isolate the corresponding gene.

One of ordinary skill in the art would merely have to substitute the protein of Stauber for Lee's urate oxidase in order to enjoy the same reasonable expectation of success disclosed in Lee. The fact that Lee states in the abstract that the method disclosed therein is "generally applicable" provides one of ordinary skill in the art with both the suggestion and the expectation of success, to substitute the Lee's urate oxidase with that of any other protein. Similar motivation exists in Wozney on page 738. Note Wozney states in the first paragraph that cloning a gene "is...of obvious utility" and that only a portion of the sequence is necessary in order to obtain the full

Serial No.: 08/444,791
Art Unit: 1806

-10-

length amino acid sequence. In fact, Wozney explicitly states that isolation and cloning of the gene is useful in determining the full length sequence of the protein.

Consequently, determination of the full length sequence alone constitutes sufficient motivation to clone the gene corresponding to the protein of interest.

13. Applicant is reminded that the translation of the non-English patent publication EP 464 533 was not considered because applicant has not complied with the requirements for information disclosure.

14. No claims are allowed.

15. Both LeMaire (5,344,915) and Smith (5,395,760) teach TNF binding protein sequences which are not the same as those set forth in fig. 19.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-4204 from 9:00 am to 5:00 pm weekdays with the exception of alternating Mondays. If the examiner cannot be reached, the supervisor, Marion Knode, may be contacted at phone number (703)308-4311.

The number for facsimile submission of papers has changed. The new fax number for Art Unit 1806 is (703) 305-7401. Please provide the serial number, application title, examiner's name, and art unit on the fax cover sheet to expedite clerical processing. In addition, all cover sheets should be marked **DRAFT** or **OFFICIAL** as appropriate.

Any informal communications of a **nonconfidential** nature can be communicated to Examiner Nisbet electronically at the following address, tnisbet@uspto.gov.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TMN
25 January 1996


PAULA K. HUTZEEL
PRIMARY EXAMINER
GROUP 1800